

Evaluation of Osveral efficacy in reducing ferritin levels in patients with thalassemia major

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ABSTRACT

Background: Beta thalassemia is one of the inherited blood diseases in which the production of specific chains in hemoglobin decreases. Esfarlar is a salt which is used in these patients as a single dose per day. Since it is prescribed orally, it is easier to tolerate the drug and control the serum iron level of the patient. The aim of this study was to evaluate the efficacy of Osveral in reducing ferritin levels in patients with thalassemia major.

Methods: This quasi-experimental study was performed on 48 patients with thalassemia major who referred to Bu-Ali hospital for receiving blood. At the beginning of the study, the required data were collected along with patients' tests including hemoglobin, ferritin, TSH, T4, CBC diff, BUN AST, ALT, BS and creatinine CBC diff. The Osveral drug was prescribed and the patients were evaluated monthly for up to 6 months on the basis of complications. In the first three months after the start of the drug, the serum ferritin level was measured, the dose was adjusted and 6 months after late, the previous tests were again requested, and the auditory and visual examinations were performed, and the information entered the checklist. Data were analyzed using SPSS statistical software.

Results: Among all patients, 27 (56.2%) were male and the rest were women with a mean age of 22.22 ± 8.77 years. The results showed that during one year of study, hemoglobin level increased and ferritin level decreased significantly, and other parameters didn't show significant difference. Nausea and vomiting were the most common complications among patients, which was higher after Osveral than before receiving Osveral.

Conclusions: Results showed that Osveral is effective in reducing the level of ferritin in patients with thalassemia major, but control of hematuria is recommended when using this drug.

Keywords: Ferritin, Major thalassemia, Osveral

INTRODUCTION

Beta-thalassemia is one of the hereditary blood disease in which the rate of beta chain generation decreases in hemoglobin.¹ Today, by advancing in treatment and care of children with major thalassemia, their lifetime has been increased and regular blood injection in these patients has decreased the side effects of anemia and improved their growth and maturation.^{2,3}

Frequent blood transfusions, in spite of having a lot of clinical benefits for these patients, it can lead to inevitable side effect of Hemosiderosis and may disturb the function

of tissues as hepatic disorders, heart failure, growth disorders, hypogonadism, hypothyroidism, parathyroidism and diabetes and may cause death in second or third decade of patient's lifetime.⁴⁻⁶ Each unit of Packed RBC includes 250-300mg of iron and patients who have received more than 100 units RBC may become hemosiderotic. For preventing any above mentioned side effects, extra iron has to be removed by deironing methods which is conducted by deferoxamine but again the disorders of endocrine glands can be observed in these people and even some of these side effects have been worsen because of patient's long lifetime.

In the absence of inflammatory diseases, measuring ferritin serially is a trustable index and in fact the easiest way for evaluating the iron aggregation in body and the quality of chelator therapy which indicates the amount of iron aggregation in last three months. The decision to long-term transfusion requires the consumption of iron chelators. Deferoxamine is one of well-known iron chelators in last decade that is really applicable for these patients. This medicine can cause some prevalent side effects such as cataract, deafness, growth disorders and urticaria.⁷⁻⁹ Although this drug has a vast application but because of side effects and its usage (as subcutaneous injection), some of patients are not able to tolerate it.

It is clear that non using another chelator may cause the early death of patients.¹⁰

Deferosirox has been evaluated in more than 45 clinical trials since 2003. At first this drug known in the market with the commercial name of Exjade ®. Single-dose use of this medicine per day as 10-40 mg/kg indicated more decrease in the concentration rate of hepatic iron toward deferoxamine in adult patients and also children. Deferosirox can be well tolerated in matures, elderlies and children above 2 years old and is used once a day in the form of oral.¹¹⁻¹⁵

Osveral is the other commercial name of deferasirox which is made by an Iranian company and is used as single-dose daily. The side effects of this drug include digestive side-effects (nausea, vomiting, diarrhea, Abdominal pain, emphysema and constipation), rash and headache. This medicine should not be consumed with anti-acid drug or other chelators simultaneously.¹⁶

While Osveral is prescribed by orally and its tolerance and control of iron level of patients is done more easily, so the aim of this study was to evaluation of efficiency and side effects of Osveral in major thalassemia patients of Ardabil city.

METHODS

This study was conducted in Bu-Ali hospital in Ardabil city, Iran.

Study design

It was a quasi-experimental study. The information of each patients with the results of examination and tests of patients (hemoglobin, ferritin level, TSH, T4, CBC diff, AST BUN, ALT, BS, and creatinine CBC diff) were collected in a checklist.

Inclusion criteria

Participants with major thalassemia, age 2-62 years, ferritin level up 1000ng/dl, normal creatinine level and non-using heart drugs and not having vision or hearing problems included in the study.

Exclusion criteria

Participants with liver, kidney and heart disease, non-tolerance to lactose and age >62 years, age <2 years, severe skin rash, retinopathy, hearing loss and sensitivity to deferoxamine excluded from study.

Study tools

The study conducted on 48 patients with major thalassemia. The study patients were monthly examined during 12 month by considering drug side effects. In the first three months after receiving the drug, the serum ferritin level was measured, the dose of medicine was modified and the before examinations was checked 6 and 12 months after receiving osveral and also hearing and sight examinations is done and the information entered the check list. In order to investigate the effect of osveral in decreasing the ferritin level, all drugs were stopped if they are treating with other chelators (deferoxamine or L1).

Statistical analysis

Collected data were analyzed using analytical statistical methods such as chi-square and t-test and descriptive statistics in form of tables and figures. In all mentioned tests, the meaningful level was $p < 0.05$.

RESULTS

Of all patients, 27 were male (56.2%) and the rest were female. The average age of patients was 20.2 ± 8.8 years old and 21 patients (43.8%) were in the age range of 20-30. Most of patients with 38 cases had the blood reception interval of 3-4 weeks. 13 patients (27.1%) had history of splenectomy and 25 (52.1%) had the ferritin level in range 1000-2000 dl.

Table 1: Compare the ferritin level in follow-up time by groups.

Time	Group	Mean \pm SD (mg/dl)	p-value
Baseline	Desferal	2154.5 \pm 763	0.43
	Osveral	2056.8 \pm 814	
6 months later	Desferal	1913.6 \pm 822	0.13
	Osveral	1872.2 \pm 848	
End of study (12 months later)	Desferal	1718 \pm 736	0.025
	Osveral	1621.7 \pm 718	

The Recipients of osveral significantly had more hemoglobin level toward Recipients of desferal. Prescribed drugs had no effect on platelet level of patients and the disturbance in urinal examination of osveral receiving group was more than other group. The high rate of WBC and hemachoric in osveral receiving group significantly was more than desferal receiving group. No meaningful relationship was found between the creatinine level and the type of used drugs in patients. Both groups

had the same ferritin level at the baseline and after one year of receiving the medicine the ferritin rate in osveral receiving group had a meaningful decrease than other group (Table 1).

The side effects in osveral receiving group were meaningfully more than desferal receiving group (Table 2).

Table 2: Frequency of side-effects by groups.

Side-effects	Desferal		Osveral		p-value
	n	%	n	%	
Nausea and vomiting	3	6.3	9	18.9	0.08
Hearing loss	1	2.1	3	6.3	0.3
Skin Rash	1	2.1	3	6.3	0.3
Hematuria	3	6.3	11	23	0.03
Vision changes	1	2.1	3	6.3	0.3

DISCUSSION

In this study, during one year study of the patients, the hemoglobin level increased and the ferritin level decreased meaningfully and other parameters didn't have meaningful difference. In study of Eshghi et al, along with current study, there was a meaningful relationship between receiving osveral (iron chelator) and decrease of serum ferritin level ($p=0.001$) but in different age groups the difference was not meaningful. In Keykhai and et al. study the results indicate the meaningful changes of serum ferritin level which expresses the high efficiency of osveral + desferal medicine regime.^{17,18} In study of Pormovahed and et al, 62.8% of patients were injected deferoxamine regularly and there was a meaningful statistical difference between the average of height, weight, arm and head around in both investigated groups.¹⁹ The results indicated that the iron discharge is one of the main methods of body growth of thalassemic children in the early years of life by deferoxamine effectively and it requires the regular blood injection. It is observed in study of Ghader Rashidi et al, that the deferoxamine injection with high dose can decrease the heart symptoms in thalassemic patients considerably and improved the systolic operation meaningfully but it has no meaningful effect on diastolic operation, physical finding and ECG of patients.²⁰ Molavi et al, observed along with current study that the one-year consumption of osveral can decrease the rate of ferritin in thalassemic patients meaningfully.²¹ Taher et al. indicated that defesirox similar to other drugs has same efficiency and safety as an iron chelator in beta-thalassemic patients.²² It was observed in the study of Cappellini et al, which compared the prescription of osveral with four doses of 5, 10, 20, 30mg/dl with desferal that the rate of decrease of serum iron level in osveral receivers toward desferal was meaningful.²³ It is also expressed that the decrease rate of serum iron level increased considerably with the increase of osveral dose ($p=0.01$). It is also observed in the study of Cassinero et al, that one-year regime of

deferoxamine and osveral combination decreased significantly the serum iron level from 11.44mg/g dw to 6.54mg/g dw and serum ferritin level from 2254ng/ml to 1346ng/ml.²⁴ It was observed in Jasim et al, study that in patients receiving desferal and osveral simultaneously, the ferritin rate in one year decreased about 23.3% and in patients receiving osveral alone this rate decreased about 18%.²⁵ Arandi et al, observed that patients receiving deferoxamine + osveral in one year, the level of ferritin serum decreased from 4031 to 2416 meaningfully ($p=0.001$).²⁶ The comparison of results of current study with other studies showed that receiving osveral can decrease the rate of ferritin level and serum level meaningfully and its combination with desferal is more effective but present study showed that osveral can have more effect than desferal. In present study, nausea and vomiting are the most prevalent side-effect and in patients after receiving osveral is more than before receiving. Eshghi et al, stated that at least 36.4% of patients experienced one of the side effects.¹⁷ The most prevalent side effect of injection is the increase of serum level of creatinine and the five times increasing of level of transaminases. In Keykhai et al, study, 21% of patients experienced at least one of the side effects so that the most prevalent side-effect was increase of creatinine level.¹⁸ In Ghader rashidi et al, study no meaningful side effect was observed in deferoxamine receivers.²⁰ Taher et al. indicated that side effect was low to medium and was eliminated without any additional treatment.²² It was observed in Molavi et al study that 11.3% of patients have side-effects because of using osveral.²¹

Cappellini et al, observed that 15% of osveral receiving were with digestive symptoms and no digestive effects were seen in desferal receiving group.²² Piga et al, observed that 65.9% of osveral receiving patients are with digestive problems, 12.7% with arthropathy and in desferal receiving group, 38% of patients with digestive side effects and 14% with arthropathy ($p=0.04$).²⁷ Cassinero et al, indicated that no considerable hepatic and kidney side-effects were seen in desferal and osveral receivers.²⁴ Jasim et al, observed that there is no meaningful difference in operational tests of kidney-hepatic, the number of platelets, sight, hearing, etc. between desferal and osveral simultaneously and osveral receiving alone.²⁵ Arandi et al, observed that drug treatment therapy can not lead to drug side-effects such as increasing creatinine, hepatic enzyme and BUN.²⁶ Haghpanah et al, observed that osveral had more side-effects than desferal ($p=0.4$) and in deferoxamine group the more prevalent side effect was neurostimulation and the pain of injection.²⁸

CONCLUSION

The results showed that osveral is a portable iron chelator by patients and has effects similar to desferal in decreasing serum iron level in patients with iron overload. Osveral comparing to desferal has less side effects for patients but

it is more effective in decreasing ferritin rate and hemoglobin level in major thalassemia patients.

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REFERENCES

- Weatherall DL, Clegg JB. Thalassemia: a global public health problem. *Nat Med*. 1996;2(8):847-9.
- Najafipour F. Evaluation of endocrine disorders in patients with thalassemia major. *Int J Endocrinol Metabol*. 2008;6(2):104-13.
- Fosburg M, Nathan DG. Treatment of Cooley's anemia. *Blood*. 1990;76:435-44.
- Kliegman RM, Behrman RE, Jenson Hal B, Stanton Bonita F. *Nelson Textbook of pediatrics*. 8th ed. Philadelphia:Saunders; 2007:2034-2036.
- Najafipour F, SariSorkhabi R, Zareizadeh M, Bahrami A, Ghoddousi K, Sorkhabi R, et al. Evaluation of Endocrine Disorders in Patients with Thalassemia Major. *Iran J Endocrinol Metab*. 2008;10:35-43.
- Schwartz E, Benz EJ Jr. Thalassemia syndromes. In: Miller DR, Baehner RL, Smith CH, editors. *Smith's Blood Diseases of Infancy and childhood*. 6th ed. st. louis: Mosby; 1989:428-440.
- Rezaei M, Poor Mahmoodi A, Ghaffarian Shirazi HR, Pakbaz F. Prevalence of diabetes mellitus in Thalassemic patients referring to Cooley's centers of Kohgiluyeh and Boyerahmad. *Armaghane-Dansh J Yasuj Unive Med Sci*. 2004;9:42-35.
- Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. *N Engl J Med*. 1994;331:567-73.
- Gabutti V, Piga A. Results of long-term iron-chelating therapy. *Acta Haematol*. 1996;95:26-36.
- Arboretti R, Tognoni G, Alberti D. Pharmacosurveillance and quality of care of thalassaemic patients. *Eur J Clin Pharmacol*. 2001;56:915-22.
- Deferasirox. Available at: <http://clinicaltrials.gov/ct2/results?term=deferiasirox/> accessed on 6/17/2011
- Deferasirox. Available at: <http://www.exjade.com/index.jsp?lightbox=global-hcp/> accessed on 6/17/2011
- Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase 3 study of deferiasirox (ICL670), a once-daily oral iron chelator, in patients with b-thalassemia. *Blood*. 2006;107:3455-62.
- Taher A, El-Beshlawy A, Elalfy MS, Al Zir K, Daar S, Habr D, et al. Efficacy and safety of deferiasirox, an oral iron chelator, in heavily iron-overloaded patients with betathalassaemia: the ESCALATOR study. *Eur J Haematol*. 2009;82:458-65.
- Cappellini MD, Porter J, El-Beshlawy A, Li CK, Seymour JF, Elalfy M, et al. EPIC Study Investigators. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferiasirox in 1744 patients with transfusion-dependent anemias. *haematologica*. 2010;95.
- Deferoxamine. Available at: http://www.osvahpharma.com/index.php?module=cdk&func=loadmodule&system=cdk&sismodule=user/content_view.php&sisOp=view&id=6&ctp_id=18&cnt_id=806www.fdo.ir/Drug/Fa/Downloads/ShowSection.aspx?fid=11/ accessed on 6/17/2011.
- Eshghi P, Farahmandinia Z, Molavi M, Naderi M, Jafroodi M, Hoorfar H, et al. Efficacy and safety of Iranian made Deferiasirox (Osveral®) in Iranian major thalassemic patients with transfusional iron overload: A one year prospective multicentric open-label non-comparative study. *DARU*. 2011;19(3):35.
- Keikhaei B. Sequential Deferoxamine - Deferiasirox in Treatment of Major Thalassemia with Iron Overload; *Iranian Journal of Pediatric Hematology and Oncology Vol1. No1*.
- Pourmovahed Z, Kalani Z, Salimi T, Kargar M. Investigating the Effects of Defroxamine Injection on Physical Growth in Children with Thalassemia Major. *JSSU*. 2012;20(2):194-200.
- Rashidi GF, Kosaryan M, Karami H. Assessment of the effect of combination therapy with Deferiprone & Desferrioxamine on cardiac complications in major Thalassemia. *J Mazandaran Univ Med Sci*. 2007;17(61):12-9.
- Molavi MA, Doozandeh, Nazemi AM, Evazi R, Mansoori F. Comparison of Therapeutic Response and Complications of Oral Osveral and Injection Desfereal Chelating Agent in Patient with Thalassemia Major. *Asian J. Med. Pharm. Res*, 2013;3(3):93-7.
- Taher A, El-Beshlawy A, S. Elalfy M, Al Zir K, Daar SH, Habr D, et al. Efficacy and safety of deferiasirox, an oral iron chelator, in heavily iron-overloaded patients with b-thalassaemia: the ESCALATOR study. *European Journal of Haematology*. 2009;82:458-65.
- Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S. A phase 3 study of deferiasirox (ICL670), a once-daily oral iron chelator, in patients with β -thalassemia. *Blood*. 2006;107:3455-62.
- Cassinerio E, Orofino N, Roghi A, Duca L. Combination of deferiasirox and deferoxamine in clinical practice: an alternative scheme of chelation in thalassemia major patients. *Blood Cells Mol Dis*. 2014 Sep;53(3):164-7.
- Jasim TA, Al-Wataify A, Tarish AH. A safety and efficacy of combination therapy of def erasirox and deferoxamine versus deferiasirox for treatment of transfusional iron overload in sickle cell anemia in al-najaf and babylon province in iraq. *Med. Res. Chron*. 2014;1(1):04-10.
- Arandi N, Haghpanah S, Safaei S, Zahedi Z, Ashrafi A, Eatemadfar P. Combination therapy - deferiasirox and deferoxamine - in thalassemia major patients in

- emerging countries with limited resources. *Transfus Med*. 2015 Feb;25(1):8-12.
27. Piga A, Galanello R, Forni GL, Cappellini MD, Origa R. Randomized phase II trial of deferasirox (Exjade, ICL670), a once-daily, orally-administered iron chelator, in comparison to deferoxamine in thalassemia patients with transfusional iron overload. *Haematologica*. 2006;91:873-80. PubMed: 16818273.
28. Haghpanah S, Zarei T, Zahedi Z, Karimi M. Compliance and satisfaction with deferasirox

(Exjade®) compared with deferoxamine in patients with transfusion-dependent beta-thalassemia. *Hematology*. 2014;19(4):187-91.

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